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Association of Burn Mortality and Bacteremia

A 25-Year Review

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• The relationship between bacteremia and mortality was studied in 5882 burn patients consecutively admitted to one burn center between 1959 and 1983. Among 5877 patients with adequate data, 1481 had one or more positive blood cultures; 1529 patients died. A predictor of mortality was developed, based on data from the 4396 patients without positive blood cultures, and used to assign a discrete probability of death in the absence of bacteremia to all the patients. Comparisons were then made between observed and predicted mortality in subsets of patients with bacteremia due to (1) enteric organisms, (2) *Pseudomonas* species, (3) gram-positive organisms, or (4) yeastlike organisms, or without bacteremia. These comparisons indicate significantly increased mortality in patients with gram-negative bacteremia, an equivocal increase in patients with blood cultures positive for yeastlike organisms, and no increase attributable to gram-positive bacteremia.
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Though rarely expre ., the belief is widespread that elimination of infection would materially change the mortality observed following burn injury. Indeed, this paradigm has driven muc . of burn research for the past 30 years, but we know of no objective evaluation of its validity. In this study, we have explored the relationship between the occurrence of bacteremia and mortality in burned patients.

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Bacteremia was selected for study principally because its assessment is objective. Not all burned patients with lethal infection are bacteremic, nor are positive blood cultures exclusively confined to septic patients, but bacteremia following burn injury is well correlated with serious infection. Other possible indexes are less precise; definitive diagnosis of pulmonary infection after burns, for example, often rests on difficult clinical distinctions among pneumonia, pulmonary edema, and inhalation injury. Bacteremia is not synonymous with burn wound sepsis, though many patients with such sepsis are bacteremic. Often, however, the source of bacteremia in burned patients is equivocal, even among those who come to autopsy.

PATIENTS AND METHODS

The Study Group

Between Jan 1, 1959, and Dec 31, 1983, there were 5882 patients admitted to the US Army Institute of Surgical Research, Fort Sam Houston, Tex, for burn care. The average burn size in this population was 33.8% of total body surface, with 15% of total body surface full-thickness injury; mean age was 26.3 years. During these years, both staffing and techniques of care varied appreciably. During the first five years, topical antibacterial chemotherapy was unavailable, resuscitation was guided primarily by the classic Brooke formula, and burn wounds were managed by either exposure or dressing techniques. Early excision was little practiced, and a variety of antibiotics were used both prophylactically and therapeutically.

Topical chemotherapy of the burn wound was introduced in 1964 and has continued to the present. Mafenide acetate cream was used exclusively until 1974, silver sulfadiazine between 1974 and 1977; since 1977, mafenide acetate and silver sulfadiazine creams have been used concurrently, alternated every 12 hours in most patients. Since the introduction of topical chemotherapy, prophylactic use of systemically administered antibiotics for wound management has largely been abandoned. New antibiotics have been added to the therapeutic arsenal as they have been developed. Early use of colloids in resuscitation has been practiced less since the mid-1960s, and during the last ten years, early excision of the burn wound has been more frequently practiced. By a variety of techniques, maintenance of nutrition has received careful attention over the entire study interval.

Admissions to the institute come from all over the world. The study interval spans a war, with attendant admission of many battlefield casualties, and a long peacetime interval. The average age at admission increased from 23 years during the first ten years of the study to 30 years during the last ten. Eighty-two percent of the patients were male. Nineteen percent were children 15 years of age or younger. Surgeon-patient and staff-patient ratios varied appreciably over the study interval, as did staff experience, but the institute was never without several members with long experience in the care of burns.

Methods

Any study of bacteremia depends on the protocol governing the acquisition of blood cultures. In the years covered by this study, this protocol varied from acquisition of cultures only when the patient's clinical course suggested sepsis to routine blood culture in all patients. It is safe to assume, during the whole interval, that cultures were taken in all patients with clinical signs of sepsis. For study purposes, patients were considered bacteremic if they had one or more positive blood cultures for any species of bacteria or yeast during their hospital course.

Between 1959 and 1981, aseptically drawn 10-mL blood specimens were equally divided between paired 50-mL bottles of tryptic digest broth and thioglycolate broth for culture. Since 1981, aerobic and anaerobic examination of such specimens has been carried out using an automatic blood culture evaluating (Bactec 460) system.

Rather than detail the individual species acquired in these cultures, we have divided them into four groups: (1) enteric organisms, (2) *Pseudomonas* species, (3) gram-positive organisms, and (4) yeastlike organisms. Table 1 lists the principal observed members of these groups.

Statistical analyses were carried out using BMDP programs[1] implemented on a minicomputer (VAX-11/780). Binomial error terms were estimated using programs developed within the institute; these terms were verified by a method described by Flora.[2]

RESULTS

Among the 5882 burned patients studied, data were inadequate for five nonbacteremic surviving patients. Of the remaining 5877 patients, 1481 had one or more positive blood cultures and 1529 patients died, 873 with and 656 without bacteremia (Table 2).

Each of the four groupings of causative organisms permitted an individual binomial assignment of each patient; individual patients either did or did not have an episode of bacteremia due to some member of each group. Such

Table 1.—Principal Species in Groups

Group	Organisms (%)
1	*Providencia stuartii* (23)
	Klebsiella pneumoniae (21)
	Escherichia coli (14)
	Enterobacter cloacae (13)
	Proteus mirabilis (9)
	Enterobacter aerogenes (7)
2	*Pseudomonas aeruginosa* (91)
3	*Staphylococcus aureus* (57)
	Staphylococcus epidermidis (24)
	Bacillus species (5)
	Enterococcus species (5)
4*	Yeast (100)

*Of identified organisms, more than 95% were *Candida* species.

Table 2.—Mortality in Bacteremic and Nonbacteremic Patients

	Nonbacteremic	Bacteremic	Total
Lived	3740	608	**4348**
Died	656	873	**1529**
Total	**4396**	**1481**	**5877**

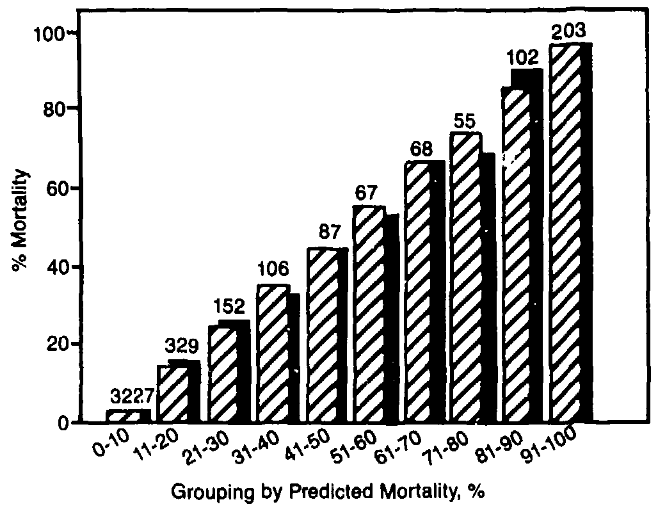

Fig 1.—Relationship between observed (solid bars) and predicted (hatched bars) mortality in patients without positive blood cultures. Number of patients in subgroup is shown at top of each bar.

Table 3.—Classification of Patients by Bacteremia*

	Groups 1 and 2 Negative	Group 1 Positive	Group 2 Positive	Groups 1 and 2 Positive
Groups 3 and 4 negative	4396 (14.2)	227 (73.1)	139 (74.8)	123 (87.0)
Group 3 positive	418 (26.0)	169 (60.0)	98 (72.4)	151 (82.8)
Group 4 positive	22 (68.2)	13 (92.3)	9 (88.9)	11 (90.9)
Groups 3 and 4 positive	27 (55.6)	34 (76.5)	18 (72.2)	22 (81.8)

*Values in parentheses are observed percentage mortality.

assignment creates 2^4 or 16 possible patient subsets, ranging from a subset without bacteremia to a subset experiencing bacteremia due to a member of each of the four organism groups at various times during the hospital stay. Table 3 gives the number of patients in each of these subsets, along with the percentage mortality observed in each subset. Raw mortality varied from subset to subset, but these differences cannot be interpreted without considering the severity of injury.

Multiple logistic regression analysis of the relationship between mortality and burn size and age (K) among the 4396 nonbacteremic patients was used to estimate an adjustment for severity of injury. This analysis yielded the following equation:

$$K = -4.9688 + 0.11404\ (\%\ \text{Burn}) - 0.23902\ (\text{Age}) + 0.68784\ (\text{Age}^2/100) - 0.44016\ (\text{Age}^3/10\,000);$$
$$PM = e^k/(1+e^k),$$

where % Burn indicates percentage of total body surface burned and PM, predicted mortality. Age is in years. All variables entered the equation at $P<.05$. The PM calculated in this manner has limits of 0 and 1 and estimates an individual probability of death; in a group of patients, each having a PM of 0.7, 70% would be expected to die. The expected number of deaths in any group is the sum of their individual PM values.

The validity of the estimator was verified by random group selection within the nonbacteremic population. The estimator was then used to assign a PM in the absence of

Table 4.—Expected Percentage Mortality in Bacteremia Groups*

	Groups 1 and 2 Negative	Group 1 Positive	Group 2 Positive	Groups 1 and 2 Positive
Groups 3 and 4 negative	14.3 (13-15)	51.2 (46-56)	48.0 (41-55)	51.5 (44-59)
Group 3 positive	26.9 (24-30)	41.9 (36-48)	46.5 (38-55)	51.0 (44-58)
Group 4 positive	55.3 (32-77)	66.8 (38-92)	63.0 (22-100)	47.5 (18-82)
Groups 3 and 4 positive	43.4 (26-63)	48.8 (35-62)	55.4 (33-78)	53.2 (32-78)

*Values in parentheses are 95% confidence intervals.

Table 5.—Ratio of Observed Mortality and Predicted Mortality in Bacteremia Groups

	Groups 1 and 2 Negative	Group 1 Positive	Group 2 Positive	Groups 1 and 2 Positive
Groups 3 and 4 negative	1.0	1.43*	1.55*	1.70*
Group 3 positive	0.97	1.44*	1.58*	1.62*
Group 4 positive	1.25	1.33*	1.33	2.00*
Groups 3 and 4 positive	1.25	1.53*	1.30	1.50*

*$P<.05$.

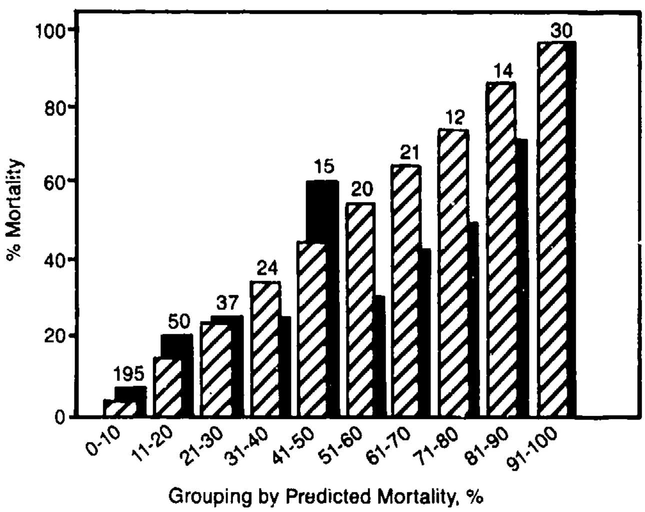

Fig 2.—Observed (solid bars) and predicted (hatched bars) mortality in patients having only gram-positive bacteremia. Among 418 patients, 112 deaths were expected in absence of bacteremia; 109 deaths occurred. Number of patients in subgroup is shown at top of each bar.

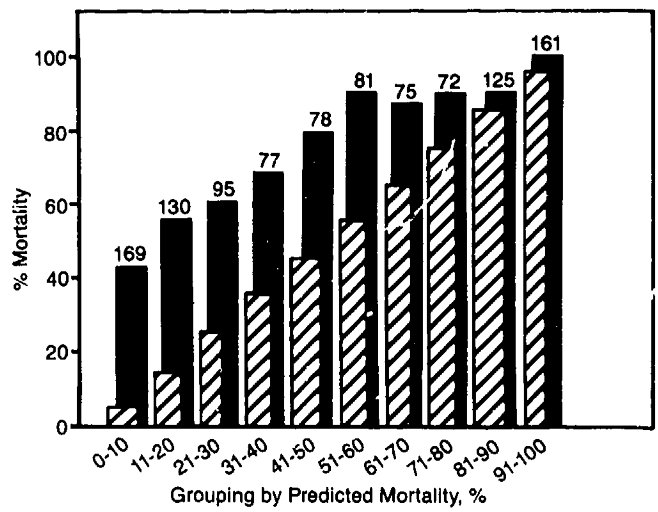

Fig 3.—Observed (solid bars) and predicted (hatched bars) mortality in patients with gram-negative bacteremia or candidemia. Expected number of deaths in these groups was 521; 792 deaths occurred. Number of patients in subgroup is shown at top of each bar.

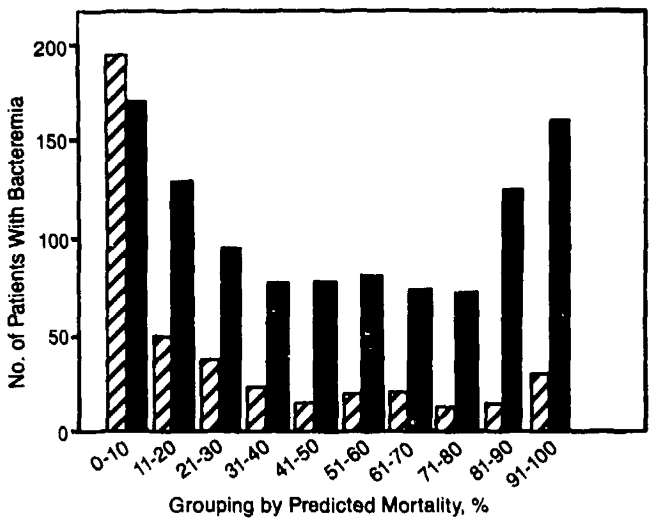

Fig 4.—Organisms causing bacteremia vary with severity of injury. Hatched bars depict number of patients having only gram-positive bacteremia; solid bars, all other patients with bacteremia.

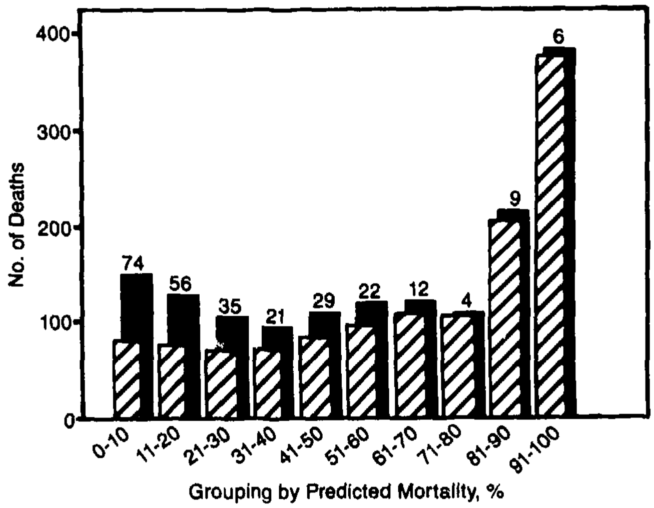

Fig 5.—Predicted (hatched bars) and observed (solid bars) deaths grouped by severity of injury. Number of unexpected deaths is shown at top of each bar.

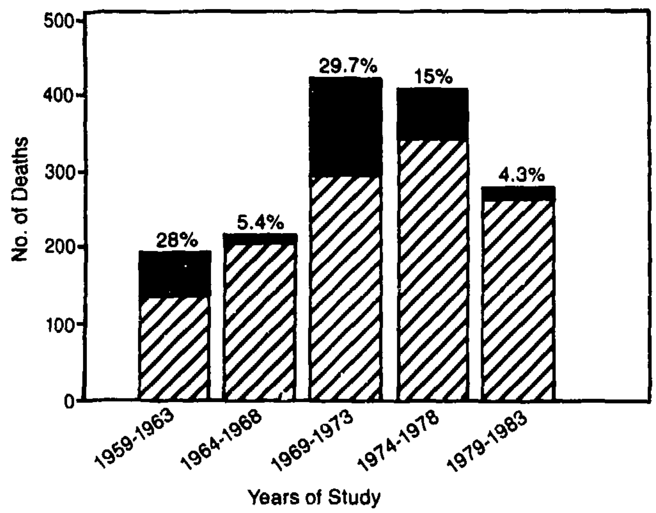

Fig 6.—Predicted (hatched bars) and observed (solid bars) deaths in five-year intervals. Values at top of each bar express unexpected deaths as percentage of all deaths in time interval.

bacteremia to each patient in the entire population. Figure 1 shows the relationship between observed mortality and predicted mortality in serial subgroups of the nonbacteremic patients. Major identifiable causes of death in the nonbacteremic patients included inhalation injury, pneumonia, pulmonary embolism, and multiple organ failure.

We next examined the difference between expected mortality in the absence of bacteremia and observed mortality in its presence; in essence, we attempted to partition patients dying of bacteremia into two groups, one in which death was anticipated whether bacteremia occurred or not, and one in which bacteremia appeared to be the cause of death. Using the individual PM values, an age- and burn-size–adjusted expected percentage mortality was calculated for each of the 16 subsets of patients (Table 4). Binomial expansion of the individual PM values within each subset was used to calculate approximate 95% confidence intervals for each expected percentage mortality. The breadth of the confidence intervals in the lower two rows of the table reflects the limited numbers of patients in those subsets.

In the absence of bacteremia, 1262 (95% confidence limit, 1220 to 1303) deaths were expected in the total population; 1529 deaths were observed. The relationship of this increase in mortality to the groups of organisms causing bacteremia in these patients is given in Table 5, which shows the ratio of observed mortality to predicted mortality in each subset. Divergence of this ratio from unity was considered significant when the observed number of deaths lay outside the 95% confidence interval for the subset. The absence of significance in four of the subsets in the lower two rows may be an artifact of subset size; each had a number of deaths near the upper confidence limit for the subset, and calculations based on pools of either the last two subsets in column 1 or the last two subsets in column 3 indicate significant enhancement of mortality ($P<.05$) in each of these pools. With the surprising exception of those patients experiencing only gram-positive bacteremia, the ratios in the bacteremic subsets were uniformly greater than 1 and were associated with a 52% increment in mortality in the group comprising the remaining 14 subsets.

The absence of increased mortality among patients experiencing only gram-positive bacteremia is puzzling but appears real. The subset includes 418 patients, a number large enough to make a size artifact improbable. In addition, no enhancement of mortality attributable to gram-positive bacteremia was observed in those subsets that included both gram-positive and gram-negative bacteremia. Figure 2 shows the relationship between observed mortality and predicted mortality in these patients across the span of severity of injury, and there is, again, little to suggest enhanced mortality. This distribution contrasts sharply with the other bacteremic groups, in which absolute increments of 40% mortality were observed in groups of patients with expected mortality below 70% and modest increases were observed in all but the most severely injured patients (Fig 3).

The distributions of the agents causing bacteremia also differed with severity of injury (Fig 4). Most of the patients having gram-positive bacteremia alone had less severe injuries, whereas the proportion of patients suffering gram-negative bacteremia or having positive blood cultures for yeastlike organisms was relatively high in all severity groups and particularly so in patients with the most severe injuries.

COMMENT

We have commented on the absence of any demonstrable impact of gram-positive bacteremia on mortality. Our data imply that such bacteremia has been successfully treated in most patients over the 25 years spanned by this study. Certainly some burned patients have died with what appeared to be lethal staphylococcal infection; this study suggests that most such patients had also sustained lethal burn injury.

By analogy, treatment of gram-negative bacteremia over this period has been less satisfactory, though in recent years, as noted below, this situation may have improved. Positive blood cultures for yeast occupy an intermediate position with respect to enhanced risk of death. The present data are too limited in scope to permit any definitive statement but are consistent with a real increase in mortality in such patients that is of lesser magnitude than that found with gram-negative bacteremia.

It is important to develop some sense of the numeric impact of bacteremic sepsis on mortality in burned patients. Seven hundred ninety-two deaths were observed among the patients having positive blood cultures for either gram-negative or yeastlike organisms in this study. In the absence of positive cultures, 521 deaths were anticipated in this group of patients. It appears that such sepsis accounted for 271 deaths over the 25 years studied. Relating this to the total patient population, the unpredicted deaths represent less than 5% of admissions; in terms of total mortality, these deaths represent a 21% increment. Figure 5 shows the distribution of these unexpected deaths with respect to severity of injury. Seventy-five percent occurred in patients whose PM in the absence of positive blood culture was less than 0.4. The enhancement of mortality in patients with a PM exceeding 0.7 was almost invisibly small. This inverse relationship runs counter to our usual sense of clinical concern and is a consequence of the distribution of severity of injury in populations of burned patients. Even in this population, which was selected to some extent for severity, 78% of the patients had PMs of 0.4 or less, yet it is in this segment of the population, where severity of injury and clinical anticipation of serious infection are least, that the greatest further inroads against mortality due to bacteremia appear possible.

The relationship of these "excess" deaths to available therapy is of interest (Fig 6). In the first five years of this study, before topical chemotherapy and with a limited antibiotic arsenal, such deaths constituted 28% of all deaths. During the succeeding five years, following the introduction of mafenide acetate cream, this value fell to 5.4%, only to rise to a second peak between 1969 and 1974 in association with persistent endemic infection due to *Providencia stuartii*. In the succeeding five years, during which silver sulfadiazine cream was used and new antibiotics were introduced, the value fell to 15%. In the most recent five years, during which wounds have been well controlled with mafenide acetate and silver sulfadiazine and more effective antibiotics have become available, we have observed a value of 4.3%.

We seem to be approaching the limit of what can be accomplished by any treatment of the sepsis indexed by bacteremia. This limiting mortality can be efficiently predicted from age and burn size alone; bacteremia seems to function as an additive complication and not as the primary determinant of the underlying lethal process. If the present level of success can be maintained, further progress in limiting burn mortality will depend more on new approaches to other fundamental problems than on better control of bacteremic infection. It is important, however, to remember that a similar minimization of unexpected mortality occurred 20 years ago, only to be lost with the proliferation of a resistant gram-negative species. The history of gram-negative infection and its treatment in burned patients suggests that we should, at most, be pleased to have the upper hand for the present and be cautious of entertaining any expectation of permanence in our present advantage.

References

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